

**REMARKS**

Claims 1 and 3-12 were pending. Claims 8-11 have been canceled. Claims 1, 3, 4 and 12 have been amended. Claim 1 has been limited to measurement of endogenous substances (see p. 10, line 21 to page 17, line 24) and the preferred SA and nucleus in the. Exogenous substance has been recited (see p. 12, lines 26-32 and original claim 10). Additionally, claim 1 has been amended to specify that in step 1a) the LIS detected is produced by direct dipole-dipole interaction between the SA and the nucleus (see p. 10, line 32 to page 11, lines 1-2). Claim 3 has been amended to delete references to endogenous substances. Claim 4 has been amended to incorporate the limitations of former claim 11, which has been canceled. Claim 12 has been amended to correct the dependency. No new matter has been added.

**Amendments to the Specification**

Applicant is grateful for the withdrawal of the objections to the specification.

**Rejections Under 35 USC §112, ¶ 1**

Claims 1 and 3-12 were rejected under 35 U.S.C. 112, first paragraph for alleged lack of enablement. The Examiner found the specification allegedly did not reasonably provide enablement for methods for all possible endogenous and exogenous species using all possible shift reagents cited in claims 10 and 11 and using MAS-NMR techniques with various nuclei. The Examiner asserted that it would require undue experimentation to perform the steps of claim 1, particularly to choose the best SA for a specific exogenous or endogenous material.

Applicants respectfully traverse. As an initial matter the claims have been substantially narrowed. They are limited to determination of the uptake of exogenous substances, for which extensive guidance is provided in the specification (in particular see page 12, line 1-17: “*Step a) selection of the shift agent*”; p12, line 19 to page 13, line 8: “*Step a): selection of nucleus* (combination)” and page 13, from line 21 to page 14, line 9: *Step c) Selection of the SA and nucleus combination*” and rationale/criteria for general guidance (see for example p. 10, line 21 to page 11, line 23) allowing generalization to measurements different than the one experimentally tested). Additionally, the claims have been amended to require that the SA comprises a lanthanide selected from a recited list and that the nucleus detectable by MAS-NMR is selected from the recited list. Thus, claim 1 has been limited to the measurement of EXO substances and to specific nuclei and SA. Furthermore the claims have been amended to clarify that LIS (Lanthanide Induced Shift) is due to a dipole-dipole interaction. Applicants submit that the claims as amended are fully enabled in view of the extensive teachings in the specification and the knowledge in the art. While they may require some experimentation, the Federal Circuit has made

clear that this is not fatal to enablement; the test is whether undue experimentation is required. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444(Fed. Cir. 1988).

Applicants submit that analysis of the factors set forth in In re Wands, 858 F.2d 731, 8 USPQ 2d 1400, 1404 (Fed Cir 1998) to be considered in determining whether undue experimentation is required ( 1) the quantity of experimentation necessary; 2) the amount of guidance presented; 3) the presence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the art and 8) the breadth of the claims), establishes that the instant claims can be practiced without undue experimentation. In particular, the instant claims have been substantially narrowed as explained above, the skill of those in the art (NMR and MAS-NMR in particular) is very high and while NMR and MAS-NMR are complicated, they are well known and relatively predictable to the skilled artisan. Indeed, as shown by the attached references at the date of filing, NMR was commonly practiced on the nuclei recited in the claims. See Exhibits "A", "B", "C", "D" and "E". Thus, one skilled in the art would be capable of using any of the recited nuclei in MAS-NMR. Moreover, the required SA were well known to the skilled artisan. Additionally, as outlined above and in Applicants prior response, the specification provides detailed guidance regarding the experimentation necessary to select a SA and nucleus combination and to practice the claimed invention to determine uptake of an exogenous substance. In particular, the specification explains that the specific combination of SA and exogenous substance nucleus must induce a LIS in order to be selected. The criteria behind this is also given at page 10, lines 26-28, i.e. they both (nucleus in the exogenous substance, EXO, and SA) have to distribute in the same cellular compartment (see for example p. 10, line 31 to p. 11, line 3, and at p. 13, lines 21 – 28). While a LIS must be empirically measured for each pair, the specification gives step by step instructions for doing so. See page 14, line 11 to page 16, line 19, which provides instruction regarding how to read traces of LIS obtained in Figures 1-4. Moreover any skilled practitioner of NMR would recognize when a LIS is induced, and thus could select the optimal pair of SA-nuclei and practice the claimed invention. Therefore, Applicants submit that both the selection of SA and nucleus pair by detecting a LIS by MAS-NMR, due to SA-nuclei interaction when in the same cell compartment (see traces...1a-f) and the practice of the claimed methods require no undue experimentation and are fully enabled.

Applicants note that on page 5 of the OA, the Examiner asserts that Applicants disclosure is directed to searching for isostructural pairs of exogenous/endogenous substances and contrast agents and that such search is unduly burdensome. Applicants respectfully submit that this is an incorrect understanding of the claimed invention (and apparently a confusion of it with the method disclosed by the Calabi reference). In contrast to the Calabi reference (described in more detail below), Applicants invention is a method of determining the uptake of any exogenous substance regardless of its structural

relation to the SA. The instantly claimed method measures the resonance of a nuclei (selected from the group consisting of  $^{13}\text{C}$ ,  $^{15}\text{N}$ ,  $^1\text{H}$ ,  $^{31}\text{P}$ ,  $^{19}\text{F}$ , deuterium, and  $^{11}\text{Bo}$ ) present in an exogenous substance and utilizes the LIS produced in such signal by a SA to measure the uptake of the exogenous substance. There is no requirement that the exogenous substance be isostructural with the SA or that it be a SA itself. Indeed, in the experimental example provided on page 21, acetylsalicylic acid, the exogenous substance whose uptake is measured, is not isostructural with Dy-BOPTA, the SA. Thus, Applicants submit that the instant claims are fully enabled and may be practiced without undue experimentation.

#### **Rejections Under 35 USC §102/103**

Claims 1, 3-7 and 10-12 were rejected under 35 U.S.C. §102(b)/103, as anticipated by or, in the alternative, as obvious over Calabi et al (J. Mag. Reson., 2002, IDS) ("Calabi"). Applicants respectfully traverse. As the Examiner admits (Office Action at p.7) Calabi is directed to a method of determining the cellular uptake of MRI contrast agents ("MRI-CA"). Thus, according to the Examiner's analysis Gd-BOPTA, Gd-DTPA or Gd-DOTA is the exogenous substance whose uptake is to be determined. However, the instant claims require that the nucleus of the exogenous substance which provides a signal detectable by MAS-NMR is selected from  $^{13}\text{C}$ ,  $^{15}\text{N}$ ,  $^1\text{H}$ ,  $^{31}\text{P}$ ,  $^{19}\text{F}$ , deuterium, and  $^{11}\text{Bo}$ , which excludes the Gd of the Calabi compounds. Thus, Calabi cannot anticipate the instant claims.

Moreover, Calabi fails to render the instant claims obvious. The instantly claimed method measures the resonance of the nuclei (selected from the group consisting of  $^{13}\text{C}$ ,  $^{15}\text{N}$ ,  $^1\text{H}$ ,  $^{31}\text{P}$ ,  $^{19}\text{F}$ , deuterium, and  $^{11}\text{Bo}$ ) present in an exogenous substance and utilizes the LIS produced in such signal by a separate SA to measure the uptake of the exogenous substance. There is no requirement that the exogenous substance be isostructural with the SA or that it be a SA itself. For example, the exogenous substance acetylsalicylic acid is not isostructural with the SA Dy-BOPTA and it is not itself a shift agent, nonetheless its uptake was determined using the claimed method (by measuring the resonance of acetylsalicylic acid's nuclei  $^1\text{H}$ , finding it undergoes a LIS induced by the SA Dy-BOPTA and detecting and measuring the CC/s in which acetylsalicylic acid distributes).

In contrast, Calabi is limited to measuring the uptake of Gd complexes (MRI-CA which are themselves SA) due to their isostructurality with the Dy-complexes. See Calabi, p. 6, lines 2-9). Indeed, as explained in the instant specification, the method of Calabi is premised on the virtually identical structure of the MRI-CA and the lanthanide shift agent used:

The rationale for this method relies on the complete isostructurality between the Gd-contrast agents (CA), which intra- or extra-cellular concentration has to be determined, and the lanthanide complex acting as shift agents (LIS agent). In other words, as both CA and LIS agent are supposed to show a very similar behavior (because of their isostructurality), the actual determinations of where the LIS agent

is, i.e. its exact intra- or extra-cellular concentration, are deemed to substantially correspond to where the CA would be and to the CA intra- or extracellular concentration, respectively.

Specification, ¶ 0061. Thus, Calabi neither teaches nor suggests the claimed method in which the uptake of an exogenous substance can be determined despite its lack of isostructurality with the SA based on measurement of the LIS induced in the signal of the nucleus of the exogenous substance. Therefore, based on Calabi one skilled in the art would have no expectation that the method disclosed therein could be used successfully to determine the uptake of any molecule, whether or not structurally identical to the lanthanide shift agent used. Consequently Calabi neither anticipates nor renders the claims obvious and Applicants request withdrawal of this rejection.

### **CONCLUSION**

In view of the preceding remarks, it is believed that the claims are in condition for allowance.

If there are any questions remaining as to patentability of the pending claims, Applicants would very much desire to have a telephonic interview. The Examiner is invited to contact Applicants' undersigned attorney at the number below.

No fee is believed to be due with the filing of this Amendment. However, if any fees are deemed necessary, the Director is hereby authorized to charge such fees to Deposit Account No. 50-2168.

Favorable action is respectfully requested.

Respectfully submitted,

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